SUPPLEMENTARY MATERIALS

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SUPPLEMENTARY MATERIALS

Study Descriptions

- 1. The Anti-Aging Study Cohort (AASC) includes middle-aged to elderly persons who were consecutive participants in the medical check-up program at the Ehime University Hospital Antiaging Center¹. This medical check-up program is provided to general residents of Ehime Prefecture, and is specifically designed to evaluate aging-related disorders, including arteriosclerosis, cardiovascular diseases, physical and cognitive functions. Clinical data used in this study were obtained from the personal medical check-up records of the participants. The ethics committees of Ehime University Graduate School of Medicine approved all study procedures, and written informed consent was obtained from all participants.
- 2. **Biobank Japan (BBJ)** includes 18,126 subjects enrolled in the BioBank Japan Project at the Institute of Medical Science, the University of Tokyo². Subjects were recruited from 12 medical institutes in Japan including Osaka Medical Center for Cancer and Cardiovascular Diseases, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Juntendo University, Tokyo Metropolitan Geriatric Hospital, Nippon Medical School, Nihon University School of Medicine, Iwate Medical University, Tokushukai Hospitals, Shiga University of Medical Science, Fukujuji Hospital, National Hospital Organization Osaka National Hospital, and Iizuka Hospital. Subject clinical information including age, gender, height, and weight was collected by a standard questionnaire. All participants provided written informed consent as approved by the ethical committees of the RIKEN Yokohama Institute and the Institute of Medical Science, University of Tokyo. Details of BBJ Type 2 diabetes (T2D) genome-wide association study (GWAS) has been described elsewhere³. Data from the Japanese T2D GWAS (2019)⁴ includes subjects from Biobank Japan (BBJ), the Japan Multi-Institutional Collaborative Cohort (J-MICC) Study, the Japan Public Health Center-based Prospective (JPHC) Study, and the Iwate Tohoku Medical Megabank Organization (ToMMo). Details of the study have been described elsewhere⁴.
- 3. The Beijing Eye Study (BES) is a population-based study that assessed the associated and risk factors of ocular and general diseases in a Chinese population⁵. The study was initialized in 2001, collected data from 4439 subjects aged ≥ 40 years from seven communities in Beijing area, where three of the communities were located in rural districts and four were located in urban districts. The BES was followed-up in 2006, with 3251 of the original subjects participating, and in 2011, with 2695 subjects returning for the follow-up examination. At the examinations in 2006 and 2011, fasting blood samples were taken for measurement of blood lipids, glucose, and glycosylated hemoglobin and for genotyping. All variables used in analyses were taken from

- examinations in 2006 or in 2011. The BES subjects were genotyped on two arrays, Illumina Human610-Quad (N = 832) and Illumina OmniExpress (N = 814).
- 4. **Amagasaki Study (CAGE-Amagasaki)** is an ongoing population-based cohort study of 5,745 individuals (3,435 males and 2,310 females), aged >18 years and recruited for a baseline examination between September 2002 to August 2003⁶.
- 5. Cardio-metabolic Genome Epidemiology (CAGE-GWAS) Network is an ongoing collaborative effort to investigate genetic and environmental factors, and their interactions affecting cardiometabolic traits/disorders among Asian populations, including the Japanese. CAGE participants were recruited in a population-based or hospital-based setting, depending on the design of member studies⁷. Fasting blood samples were collected after ≥6 hour fast.
- 6. Kita-Nagoya Genome Epidemiology Study (CAGE-KING) is an ongoing community-based prospective observation study of the genetic basis of cardiovascular disease and its risk factors⁸. The study recruited 3,975 Japanese subjects aged 50-80 years who underwent community-based annual health check-ups between May 2005 and December 2007. A subset of the KING study samples were included in the GWAS analysis.
- 7. **Cebu Longitudinal Health and Nutrition Survey (CLHNS)** is an ongoing community-based birth cohort study that began in 1983. The original study population, study design and recruitment protocols have been described in detail previously⁹. The baseline survey randomly recruited 3,327 pregnant women from the Metropolitan Cebu area, the Philippines in 1983-84 (3,080 singleton live births), and since followed them and their offspring to the present. Trained field staff conducted in-home interviews and collected anthropometric measurements at each visit. Overnight fasting blood samples for biomarker measurement and DNA extraction were obtained in 2005. Details of genotyping has been described elsewhere¹⁰.
- 8. China Health and Nutrition Survey (CHNS) is a nationwide, longitudinal survey aimed at examining economic, sociological, demographic, and health questions in a Chinese population¹¹. Briefly, a stratified probability sample with a multistage, random cluster design was used to select counties and cities within 9 diverse provinces (Guangxi, Guizhou, Heilongjiang, Henan, Hubei, Hunan, Jiangsu, Liaoning, and Shandong), stratified by income and urbanization using State Statistical Bureau definitions. A total of 4,560 households from 228 communities were then randomly selected from within each stratum. Health data was collected during seven rounds of surveys from 1991-2009.
- 9. **China Kadoorie Biobank (CKB)** is a prospective population-based cohort of 512,891 adults aged 30-79 years recruited from 10 geographically defined regions during 2004-2008¹². The baseline survey collected questionnaire data, physical measurements, and blood samples, including

- measurement of blood glucose with recording of time since last meal. Five-yearly resurveys are undertaken among a 5% randomly-selected sample of surviving participants, collecting the same information as at the baseline survey. All participants are followed for cause-specific mortality and morbidity and for any hospital admission, through linkages with registries and health insurance databases. Local, national and international ethics approval was obtained and all participants provided written informed consent.
- 10. The **Diabetic Cohort (DC)** was initiated in 2004 to investigate the role of genetic, physiological and lifestyle factors in the development of diabetes and its complications¹³. At baseline, >14,000 patients were recruited from primary care facilities in Singapore. Retrospective medical records were obtained five years prior to recruitment. Medical records of >6,000 participants who are being seen at the National Healthcare Group (NHG) polyclinics have been linked to the cohort data up to 2016. From 2011 to 2016, these participants were invited for a first follow-up and a second revisit has been initiated since 2017. Details of T2D GWAS using DC cases and SP2 controls has been described elsewhere¹⁴.
- 11. Singapore Prospective Study Program (SP2) comprised 6,968 participants in total, of the ages of between 24 and 95 years from four previous cross-sectional studies^{15,16}. Each of these studies sampled randomly from the Singapore population with a disproportionate sampling scheme to increase the sample sizes of the minority ethnic groups (Malays and Asian Indians). In addition, 10,747 more participants were invited to participate in a follow up study from 2003 to 2007, of which 5,157 people completed the questionnaire and clinical examination.
- 12. The **Health Examines** (HEXA) cohort is one of the KoGES (The Korean Genome and Epidemiology Study) population-based cohorts which were initiated in 2004 aiming to identify risk factors of life-style related complex diseases such as type 2 diabetes, hypertension, and dyslipidemia¹⁷. Detailed information of HEXA cohort has been described elsewhere¹⁷. Briefly, a total of 173,357 participants aged >= 40 years were recruited from the national health examinee registry. As part of Korea Biobank Array (KBA) project, at the end of 2017, about 100K samples were genotyped using KBA¹⁸. Design, contents, and quality control procedures of KBA have been described elsewhere¹⁸.
- 13. The **Cardiovascular Disease Association** (CAVAS) cohort is one of the KoGES population-based cohorts which were initiated in 2004 aiming to identify risk factors of life-style related complex diseases such as type 2 diabetes, hypertension, and dyslipidemia. Detailed information of HEXA cohort has been described elsewhere¹⁷. Briefly, a total of 28,338 participants aged >= 40 years were recruited from community-dwellers of rural area. As part of Korea Biobank Array project,

- at the end of 2017, about 20K samples were genotyped using KBA. Design, contents, and quality control procedures of KBA have been described elsewhere¹⁸.
- 14. The Hong Kong T2D Registry (HKDR) was established in 1995 as a quality improvement program at the Prince of Wales Hospital¹⁹. Patients referred to the hospital for comprehensive assessment of metabolic control and diabetes complications were enrolled. Referral sources included regional public community clinics, general practitioners, hospital-based clinics, and patients discharged from the Prince of Wales Hospital. Patients were excluded if they were non-Chinese in ethnicity or had type 1 diabetes as defined by acute presentation with diabetic ketoacidosis, heavy ketonuria or continuous requirement of insulin within 1 year of diagnosis, or if unknown diabetes type. The healthy control cohort consisted of 517 subjects from 2 sources: a) 327 healthy adults from a territory-wide health awareness and promotion program who were randomly selected by stratified random sampling with computer-generated codes in accordance to the distribution of occupational groups and hospital staff²⁰; and b) 190 individuals without diabetes who were recruited from the community for pharmacogenetics studies in hypertension or hyperlipidaemia²¹.
- 15. **Korea Association Resource (KARE)** is a part of the Korean Genome Analysis Project (KoGAP) which was initiated in 2007 to discover variants associated with Type 2 Diabetes (T2D) and numerous complex traits. Detailed information has been described elsewhere²². Briefly, a total of 10,038 participants aged 40 to 69 were recruited from two population-based cohorts comprising the rural Ansung (n=5,018) and urban Ansan (n=5,020) cohorts. The two KARE cohorts were established as part of the Korean Genome Epidemiology Study (KoGES)¹⁷. All samples were genotyped with Affymetrix Genome-Wide Human SNP array 5.0. The lipid levels were measured in a fasting state.
- 16. The Multi-Ethnic Study of Atherosclerosis (MESA) is a longitudinal study of the characteristics of subclinical cardiovascular disease (disease detected non-invasively before it has produced clinical signs and symptoms) and the risk factors that predict progression to clinically overt cardiovascular disease or progression of the subclinical disease. MESA researchers study a diverse, population-based sample of 6,814 asymptomatic men and women aged 45-84. Thirty-eight percent of the recruited participants are white, 28 percent African-American, 22 percent Hispanic, and 12 percent Asian, predominantly of Chinese descent. In MESA, fasting blood samples were collected at baseline, processed, and stored at −70°C.
- 17. The **NAGAHAMA Study** is a community-based longitudinal study in Japan. Participants in the Nagahama study were recruited from general population of Nagahama, a rural city of 125,000 inhabitants located in central Japan (N = 9,764)²³. Community residents, aged between 30 and

- 74 years at recruitment, who were living independently without physical impairment or dysfunction, were eligible. All study procedures were approved by the Ethics Committee of Kyoto University Graduate School of Medicine and the Nagahama Municipal Review Board. Written informed consent was obtained from all participants.
- 18. **Shanghai Breast Cancer Study (SBCS)** included two recruitment phases, as described in detail elsewhere^{24,25}. During the initial phase (SBCS-I), 1,459 breast cancer patients and 1,556 controls were recruited between 1996 and 1998 through a rapid case-ascertainment system, and the population-based Shanghai Cancer Registry. Blood samples were obtained from 1,193 (82%) cases and 1,310 (84%) controls. The second phase of participant recruitment (SBCS-II) was conducted between 2002 and 2005 using a protocol similar to the one used during the initial phase. A total of 1,989 incident cases and 1,918 community controls were recruited. The majority of cases (n=1,932, 97.1%) and controls (n=1,857, 96.8%) provided a blood sample or an exfoliated buccal cell sample.
- 19. **Shanghai Women's Health Study** (SWHS) is a population-based cohort study of approximately 75,000 women who were aged 40-70 years at study enrollment (1997-2000) and resided in seven geographically defined communities²⁶. 56,832 individuals (75.8%) provided a blood sample. A subset of participants who were selected for nested case-control studies of cancer and diabetes with both lipid profile data and GWAS data available were included in this study.
- 20. **Singapore Chinese Eye Study (SCES)** is a population-based, cross-sectional study to investigate the epidemiology of eye diseases and traits in Singaporean Chinese. Sampling was performed in the 15 residential districts, and included 3,353 Chinese²⁷. Details of genotyping in SCES have been described elsewhere^{28,29}.
- 21. **Singapore Chinese Health Study (SCHS)** is a cohort study of 63,257 Singaporean Chinese (Hokkien or Cantonese dialect group) aged 45-74 years, and residing in public housing estates^{30,31}. Recruitment and assessment of baseline diet and other interviews took place in the participant's home from 1993 to 1998. Blood was collected in 28,439 participants between 2000 and 2005. The cohort has been followed up for mortality and morbidity through regular record linkage with the Singapore Cancer Registry, the Hospital Discharge Summary Database and the Singapore Registry of Births and Deaths through collaboration with the Ministry of Health. Details of the T2D GWAS have been described elsewhere³¹.
- 22. **Singapore Malay Eye Study (SiMES)** is a population-based, cross-sectional study to investigate the epidemiology of eye diseases and traits in Singaporean Malays³². 3,280 Malay adults living in 15 residential districts in the southwestern part of Singapore were recruited. Details of Type 2 diabetes (T2D) genome-wide association study (GWAS) has been described elsewhere¹⁴.

- 23. **Seoul National University Hospital (SNUH)** study is a hospital based cohort study to investigate the genetic etiology of diabetes and its complications in Koreans. A total of 2,100 T2D cases and 911 controls participated in this study. T2D participants were enrolled from Diabetes Clinic at Seoul National University Hospital and non-diabetic control participants were enrolled from Health Examination Clinic at the same hospital. The details of this study have been described elsewhere³³.
- 24. **Samsung Medical Center (SMC) study** is a hospital-based study of 331 cases and 118 controls. The age of subjects was mostly ranged between 30-80 years. All individuals provided a blood sample. All DNA samples were genotyped with Affymetrix NSP 250K. SNP imputation was carried out using IMPUTE2 program. The 1000G Phase3 data were used as a reference panel for SNP imputation.
- 25. The TAlwanmetaboCHIp consortium (TaiChi) was formed through a collaborative effort between investigators based in the U.S. and Taiwan. The TaiChi consortium consists of 7 studies that collaborated initially in a large scale metabochip study, and became an ongoing consortium for studies of cardiometabolic disease in the Chinese population in Taiwan. The consortium's main aim is to identify genetic determinants of atherosclerosis and diabetes related traits in East Asians, and to fine map validated loci identified in other race/ethnic groups. The main academic sites in Taiwan include Taipei and Taichung Veteran's General Hospitals (VGH), National Health Research Institute (NHRI), Tri-Service General Hospital (TSGH), and National Taiwan University Hospital (NTUH). The main academic sites participating in the TaiChi consortium from United States include Stanford University School of Medicine in Stanford, California; Hudson-Alpha Biotechnology Institute in Huntsville, Alabama; and Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center in Torrance California. There are 7 principal cohorts that consisted of in total 11,859 samples. The detailed description of each cohort has been published elsewhere³⁴. The seven studies included the following: 1) Taiwan Diabetes and RelAted Genetic COmplication (Taiwan DRAGON), a cohort study of type 2 diabetes at Taichung Veterans General Hospital (Taichung VGH) in Taiwan, with participants including individuals with either newly diagnosed or established diabetes (subjects with hyperglycemia who did not meet diagnostic criteria for type 2 diabetes were not included); 2) Healthy Aging Longitudinal Study in Taiwan (HALST), a population based epidemiologic study of older adults living in all major geographic regions of Taiwan established by the Taiwan National Health Research Institutes (NHRI); 3) Stanford-Asian Pacific Program in Hypertension and Insulin Resistance (SAPPHIRe), a family based study established in 1995 with an initial goal of identifying major genetic loci underlying hypertension and insulin resistance in East Asian populations, with Taiwanese

subjects participating in the TaiChi consortium; 4) TAiwan Coronary and Transcatheter intervention (TACT), a cohort study that enrolled patients with angina pectoris and objective documentation of myocardial ischemia who underwent diagnostic coronary angiography and/or revascularization any time after October 2000 at the National Taiwan University Hospital (NTUH); 5) Taichung CAD study (TCAD), includes patients with a variety of cardiovascular diseases who received care at the Taichung Veterans General Hospital (Taichung VGH), i.e. specifically individuals who were hospitalized for diagnostic and interventional coronary angiography examinations and treatment; 6) Taiwan Coronary Artery Disease GENetic (TCAGEN), a cohort study that enrolled patients undergoing coronary angiography or percutaneous intervention at the National Taiwan University Hospital (NTUH) in the setting of either stable angina pectoris or prior myocardial infarction; 7) Taiwan US Diabetic Retinopathy (TUDR) enrolled subjects with type 2 diabetes who received care at Taichung Veteran General Hospital (Taichung VGH), and a small number of subjects from Taipei Tri-Service General Hospital (TSGH); TUDR subjects underwent a complete ophthalmic and fundus examination to carefully document the presence and extent of retinopathy. From these 7 studies, samples for over 1,800 subjects were selected based on completeness of standard metabolic phenotyping and knowledge of cardiac disease status, to undergo GWAS genotyping with the Zhonghua chip (TaiChi-G).

26. The **Taiwan T2D Study (TWT2D)** includes a total of 2,798 unrelated individuals with T2D, age > 20 years, recruited from China Medical University Hospital (CMUH), Taichung, Taiwan; Chia-Yi Christian Hospital (CYCH), Chia-Yi, Taiwan; and National Taiwan University Hospital (NTUH), Taipei, Taiwan. The controls were randomly selected from the Taiwan Han Chinese Cell and Genome Bank. Details of T2D GWAS has been described elsewhere³⁵.

Supplementary Table Legends

Supplementary Table 1. Type 2 diabetes ascertainment criteria of studies included in East Asian association meta-analysis.

Supplementary Table 2. Sample characteristics of East Asian studies

Supplementary Table 3. Study-level quality control, pre-phasing, imputation and association analyses

Supplementary Table 4. Lead variants associated with type 2 diabetes in East Asian sex-combined BMI-unadjusted and BMI-adjusted meta-analyses

Supplementary Table 5. Summary statistics of multiple distinct type 2 diabetes association signals at novel and known loci in East Asian BMI-unadjusted sex-combined meta-analysis

Supplementary Table 6. Lead variants associated with type 2 diabetes in East Asian sex-specific meta-analyses

Supplementary Table 7. Summary of association results from East Asian BMI-unadjusted sexcombined meta-analysis and DIAMANTE European meta-analysis (Data used to generate Figure 2) **Supplementary Table 8.** Lookups of novel East Asian variants in other ancestries (European, South Asian, Hispanic and African American)

Supplementary Table 9. Comparison of East Asian 189 sex-combined T2D-associated lead variants with DIAMANTE European meta-analysis

Supplementary Table 10. Associations of 92 East Asian associated lead variants from Supplementary Table 9 with other metabolic traits and outcomes

Supplementary Table 11. eQTLs lookups for 92 East Asian associated lead variants from Supplementary Table 9

Supplementary Table 12. Biological candidate genes at selected loci with evidence of association with T2D in East Asians

Supplementary Table 13. Description of gene(s) identified as candidate genes for T2D-associated loci

Web Resources

Pre-imputation preparation and quality control: http://www.well.ox.ac.uk/~wrayner/tools/

Pre-phasing: SHAPEITv2/v2.3,

https://mathgen.stats.ox.ac.uk/genetics_software/shapeit/shapeit.html

Pre-phasing: Eagle v2, https://data.broadinstitute.org/alkesgroup/Eagle/

Imputation: MACHv1.0, minimac3/4, Michigan Imputation Server,

https://imputationserver.sph.umich.edu/index.html

Imputation: IMPUTEv4, https://jmarchini.org/impute-4/

Association: EPACTSv3.3 (FIRTH, EMMAX), https://github.com/statgen/EPACTS

Association: RVTESTSv2, https://github.com/zhanxw/rvtests

Association: SNPTESTv2.5, https://mathgen.stats.ox.ac.uk/genetics_software/snptest/snptest.html

Association: mach2datv1.0.24, http://csg.sph.umich.edu/yli/software.html

Association: BOLT-LMMv2.3, https://data.broadinstitute.org/alkesgroup/BOLT-LMM/

Meta-analysis: METALv2011-03-25, http://csg.sph.umich.edu/abecasis/metal/

Meta-analysis: GWAMAv2.2.2, https://genomics.ut.ee/en/tools/gwama

Analysis of GWAS statistics: GLDSCv1.01, https://github.com/bulik/ldsc

Conditional analysis: GCTAv1.91.5, https://cnsgenomics.com/software/gcta/#Overview

Visualization: LocusZoom1.4 http://locuszoom.org/

Resource: Type 2 Diabetes Knowledge Portal, http://www.type2diabetesgenetics.org

Resource: GTEx Portal, https://gtexportal.org/home/

Resource: Parker lab Islet Browser, http://theparkerlab.org/tools/isleteqtl/

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